Gastroenterology 2020;159:1526–1532

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Update on Small Intestinal Bacterial Overgrowth: Expert Review

Eamonn M. M. Quigley,[1] Joseph A. Murray,[2] and Mark Pimentel[3]

[1]Lynda K. and David M. Underwood Center for Digestive Disorders, Houston Methodist Hospital and Weill Cornell Medical College, Houston, Texas; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; and [3]Medically Associated Science and Technology Program, Cedars-Sinai, Los Angeles, California

DESCRIPTION: Thanks to ready access to hydrogen breath testing, small intestinal bacterial overgrowth (SIBO) is now commonly diagnosed among individuals presenting with a variety of gastrointestinal and even nongastrointestinal symptoms and is increasingly implicated in lay press and media in the causation of a diverse array of disorders. Its definition, however, remains controversial and true prevalence, accordingly, undefined. The purpose of this review, therefore, was to provide a historical background to the concept of SIBO, critically review current concepts of SIBO (including symptomatology, pathophysiology, clinical consequences, diagnosis and treatment), define unanswered questions and provide a road map toward their resolution. **METHODS:** Best Practice Advice statements were developed following discussion by the 3 authors. Two authors each developed text around certain Best Practice Advice based on a review of available literature. All 3 authors reviewed the complete draft and after discussion, redrafting, and further review and revision, all of the authors agreed on a final draft. **BEST PRACTICE ADVICE 1:** The definition of SIBO as a clinical entity lacks precision and consistency; it is a term generally applied to a clinical disorder where symptoms, clinical signs, and/or laboratory abnormalities are attributed to changes in the numbers of bacteria or in the composition of the bacterial population in the small intestine. **BEST PRACTICE ADVICE 2:** Symptoms traditionally linked to SIBO include bloating, diarrhea, and abdominal pain/discomfort. Steatorrhea may be seen in more severe cases. **BEST PRACTICE ADVICE 3:** There is insufficient evidence to support the use of inflammatory markers, such as fecal calprotectin to detect SIBO. **BEST PRACTICE ADVICE 4:** Laboratory findings can include elevated folate and, less commonly, vitamin B-12 deficiency, or other nutritional deficiencies. **BEST PRACTICE ADVICE 5:** A major impediment to our ability to accurately define SIBO is our limited understanding of normal small intestinal microbial populations—progress in sampling technology and techniques to enumerate bacterial populations and their metabolic products should provide much needed clarity. **BEST PRACTICE ADVICE 6:** Controversy remains concerning the role of SIBO in the pathogenesis of common functional symptoms, such as those regarded as components of irritable bowel syndrome. **BEST PRACTICE ADVICE 7:** Management should focus on the identification and correction (where possible) of underlying causes, correction of nutritional deficiencies, and the administration of antibiotics. This is especially important for patients with significant maldigestion and malabsorption. **BEST PRACTICE ADVICE 8:** Although irritable bowel syndrome has been shown to respond to therapy with a poorly absorbed antibiotic, the role of SIBO or its eradication in the genesis of this response warrants further confirmation in randomized controlled trials. **BEST PRACTICE ADVICE 9:** There is a limited database to guide the clinician in developing antibiotic strategies for SIBO, in any context. Therapy remains, for the most part, empiric but must be ever mindful of the potential risks of long-term broad-spectrum antibiotic therapy.

Small intestinal bacterial overgrowth (SIBO) is increasingly recognized among patients presenting to a gastroenterologist; providing the impetus to critically evaluate methods for its recognition. Modern molecular techniques, such as next-generation sequencing, have, to date, focused on stool samples, but new studies are beginning to reveal the detailed composition of the small bowel microbiome. In this Best Practice Advice article, we examine the background to our current concept of SIBO and discuss persisting controversies.

Best Practice Advice 1

The definition of SIBO as a clinical entity lacks precision and consistency; it is a term generally applied to a clinical disorder in which symptoms, clinical signs, and/or laboratory abnormalities are attributed to changes in the numbers of bacteria or in the composition of the bacterial population in the small intestine.

The origins of the term *small intestinal bacterial overgrowth* lie in a literature exploring causes of malabsorption among individuals with surgically created blind loops, intestinal fistula, jejunal diverticulosis, and intestinal pseudo-obstruction.[1] In elegant studies, the ability of a Gram-negative flora of presumed colonic origin to metabolize amino acids, deconjugate bile acids, consume vitamin B-12, synthesize folic acid, and injure the small intestinal mucosa was demonstrated and a scientific basis for the resultant malabsorption syndrome provided.[2–4] Coliforms and *Escherichia coli*, in particular, emerged as prime suspects. Clinical improvement in, or resolution of, symptoms with antibiotics clinched the diagnosis.

The search for a more tangible, quantitative definition drew on 2 sources, intubation studies of the normal proximal small intestine[5] and an examination of relationships

Abbreviations used in this paper: CH_4, methane; CFU, colony-forming unit; H_2, hydrogen; IBS, irritable bowel syndrome; SIBO, small intestinal bacterial overgrowth.

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2020.06.090

Table 1. Diseases and Disorders Associated With Small Intestinal Bacterial Overgrowth—A Pathophysiological Approach

Abnormal small intestinal motility	Anatomic abnormalities	Hypochlorhydria	Immune deficiency	Multifactorial	Relationship to SIBO unclear
Diabetic autonomic neuropathy	Small intestinal diverticulosis	Post-surgical	Inherited immune deficiencies (eg, common variable immunodeficiency	Chronic pancreatitis	Rosacea
Systemic sclerosis/ scleroderma	Surgically-induced alterations in anatomy (Billroth II gastrectomy, bariatric surgery, end-to-side anastomosis)	Long-term acid suppression	Acquired immune deficiency (eg, AIDS, severe malnutrition)	Celiac disease	Interstitial cystitis
Amyloidosis				Diabetes mellitus	Restless legs syndrome
Hypothyroidism				Tropical sprue	Parkinson's disease
Idiopathic intestinal pseudo-obstruction				Crohn's disease	Erosive esophagitis
Acromegaly				Cystic fibrosis	Severe obesity
Gastroparesis				Intestinal failure	Irritable bowel syndrome
Myotonic muscular dystrophy	Strictures (Crohn's disease, radiation, surgery)			Radiation enteropathy	
Chronic opiate use	Blind loops			Liver disease	
Long-standing use of motility-suppressing drugs	Gastrocolic or jejunocolic fistula			End-stage renal disease	
	Ileocecal valve resection			The elderly	

between bacterial numbers in the proximal jejunum and a variety of parameters indicative of, or linked to, the malabsorption syndrome.[6] From these initial studies the now time-honored criterion of $>10^5$ bacteria/mL of jejunal fluid emerged as the diagnostic standard for SIBO. This allowed clinicians to look beyond the confines of a classical malabsorption syndrome and explore the contribution of SIBO to other clinical scenarios.[7] The widespread application of jejunal aspiration was limited by its invasive nature, problems with contamination, and challenges in bacterial culture (detailed below). The modern era of SIBO was ushered in by the advent of hydrogen (H_2) breath tests.[8] Initially employed in the diagnosis of carbohydrate malabsorption, H_2 breath tests were soon applied to measure orocecal transit and detect bacterial overgrowth.[9] Due to their simplicity and acceptability, glucose and lactulose breath tests came to dominate the field; they are the basis for virtually all of the recent literature on SIBO.[10] They came with baggage—issues such as variability in study protocol, interference from confounding factors, and an ongoing debate on diagnostic cutoffs continue to haunt us and preclude a universally accepted definition of SIBO based on breath testing. Pending the precise enumeration and characterization of the microbial population of the normal small intestine,[11] and mindful of all of the limitations discussed above, a very recent definition, which seems to bring us back to where we began, seems most appropriate: "the presence of excessive numbers of bacteria in the small bowel, causing gastrointestinal symptoms."[12]

Best Practice Advice 2

Symptoms traditionally linked to SIBO include bloating, diarrhea, and abdominal pain/discomfort. Steatorrhea can be seen in more severe cases.

What should prompt a search for the presence of SIBO? No one would contest the causative link between SIBO and maldigestion and malabsorption as seen, for example, in the presence of jejunal diverticulosis or enterocolonic fistulae. Here, the ability to suspect and diagnose SIBO is largely dependent on the ability to appreciate context; an awareness of the disorders and clinical scenarios associated with risk for SIBO (Table 1) is critical. In the very elderly, SIBO has been recognized as an important cause of otherwise unexplained diarrhea and weight loss.[7] As an indicator of the relative contributions of various factors to SIBO, one large retrospective series based on duodenal aspirates obtained from patients under investigation for a variety of problems, found that the main risk factors for SIBO were older age, steatorrhea, and the use of narcotics; significantly associated disorders were inflammatory bowel disease, chronic pancreatitis, and jejunal diverticulosis.[13]

The various clinical entities listed in Table 1 taken in aggregate account, we suspect, for a small minority of those diagnosed with SIBO today; what prompts the search for SIBO in the rest? This question can be addressed in 1 of 2 ways. First, we can look for associations, preferably in prospective studies of unselected individuals, between SIBO and certain clinical presentations. Second, we can examine response rates to the eradication of SIBO. For the first we rely mostly on retrospective case series—data that clearly has an acquisition bias; why did the clinician order the test in the first place? The second source is equally problematic, as there have been few high-quality clinical trials and eradication regimens are far from universally effective.[14]

There are 2 sources of data to address associations between SIBO and symptoms, populations with known risk factors for SIBO and studies on individuals with unexplained gastrointestinal symptoms. Although recent literature

attests to the occurrence of SIBO at higher rates than control subjects among individuals with a host of underlying conditions (Table 1), correlations with clinical features, such as nutritional status and outcomes, are far from consistent—SIBO has even been linked with obesity.[15]

Are there clinical predictors of SIBO in the various disease states to which it has been linked? In Crohn's disease, SIBO has been associated with disease phenotype, namely, fibrostenotic disease and prior surgery, especially resection of the ileocecal valve and, in cirrhosis, with complications such as encephalopathy and spontaneous bacterial peritonitis.

What then of predictors of SIBO in the much larger patient population with "functional"/unexplained gastrointestinal symptoms? Here the data are equally uninformative. SIBO has been reported to be more common in irritable bowel syndrome (IBS)[16] and methane (CH_4) production linked to constipation. However, some studies failed to document any relationships between IBS or its various clinical features and the presence of SIBO.[17] For the most part, diarrhea or "gas," but not bloating, seem to be the most predictive symptoms of SIBO in IBS.

To summarize:

1. In those predisposed to SIBO due to anatomic, pathologic, pharmacologic, or other changes that promote stasis or recirculation of colonic contents and/or impaired resistance to bacteria, SIBO will lead to diarrhea and can progress to a full-blown malabsorption syndrome.
2. Relationships between SIBO and symptoms in those without obvious predisposing factors are more tenuous and symptoms are weakly predictive at best. Contrary to common belief, diarrhea and not bloating has the strongest association with SIBO.

Best Practice Advice 3

There is insufficient evidence to support the use of inflammatory markers, such as fecal calprotectin, to detect SIBO.

Commonly performed laboratory tests will prove to be normal in most individuals considered to have SIBO today. In severely contaminated individuals, mucosal injury can occur and result in loss of brush border enzymes, leading to carbohydrate malabsorption and, through damage to the epithelial barrier, a protein-losing enteropathy. Bacterial competition with the host for luminal protein can also contribute to hypoproteinemia and edema. In severe SIBO, inflammation will develop, however, attempts to detect SIBO using levels of calprotectin in feces have provided mixed results. Although some failed to detect elevated levels in association with SIBO,[18] studies on individuals with scleroderma[19] and Crohn's disease[20] suggested that elevated levels were a valuable indicator of its presence.

Best Practice Advice 4

Laboratory findings can include elevated folate and, less commonly, vitamin B-12 deficiency or other nutritional deficiencies.

In SIBO, several factors conspire to cause B-12 deficiency: the consumption of cobalamin by anaerobes, malabsorption of the vitamin due to competitive binding with cobalamin from bacterially generated metabolites of cobalamin at the ileal receptor, and in more severe overgrowth, mucosal injury involving the binding site. Bacterial utilization of vitamins has also been invoked in the development of thiamine and nicotinamide deficiency. Deconjugation of bile acids and consequent depletion of the bile acid pool will lead to maldigestion of fat and fat-soluble vitamins with resultant steatorrhea and fat-soluble vitamin deficiencies. Although a resultant vitamin-K–responsive coagulopathy has been described in association with SIBO,[21] bacterial production of vitamin K, combined with enhanced absorption of the vitamin due to greater permeability, can serve not only to sustain but even increase vitamin K levels to a degree that warfarin dose might need to be adjusted to maintain therapeutic anticoagulation.[22] Bacterial synthesis of folic acid may result in the unusual combination of high folate and low B-12 levels.

Best Practice Advice 5

A major impediment to our ability to accurately define SIBO is our limited understanding of normal small intestinal microbial populations—progress in sampling technology and techniques to enumerate bacterial populations and their metabolic products should provide much needed clarity.

Although the last decade has seen an explosion in research into the gut microbiome, the small bowel microbiome has not been well defined even by more basic microbial techniques, such as culture.

Differentiating Normal From Abnormal Small Intestinal Microbial Populations

In the last 2 years, there has been an effort to understand the small bowel microbiome as it relates to SIBO and other conditions. The challenge here is that it is virtually inevitable that there will be a change in how SIBO is defined, depending on the techniques used (eg, culture vs next-generation sequencing). Most importantly, these efforts will need to associate microbial data with patient symptoms.

The centrality of quantitative intestinal cultures to the definition of SIBO has been challenged.[23] A recent consensus on breath testing and gastrointestinal disorders re-evaluated definitions of SIBO based on the quantitative culture of small intestinal aspirates and recommended a new threshold at $>10^3$ colony-forming units (CFU)/mL coliforms on fresh aspirate culture.[10] This change was based on a comprehensive assessment of the literature that revealed that bacterial levels in normal subjects rarely exceed 10^2 CFU/mL with the much higher threshold of $>10^5$ CFU/mL derived from subjects with altered intestinal anatomy.[23]

The details of the actual technique of aspirate and culture also deserve careful consideration. Obtaining a clean uncontaminated sample can be challenging. Duodenal aspiration requires invasive techniques, such as upper

endoscopy, to access the small bowel. In addition, it is vital that the sample is acquired without contamination from oral flora, as the scope passes through the mouth. Standardized quantitative methods of small intestinal cultures have long resided in a few academic medical centers with the expertise to do such cultures. They were not easy to reproduce in community-based microbiology laboratories.

More reliable techniques for small bowel aspiration, culture, and sequencing have now emerged. In a recent study using a double-lumen custom protected catheter, samples were obtained in a manner that mitigated the likelihood of contamination by bacteria from the upper gastrointestinal tract when passing the catheter through the scope. This study also determined that the traditional handling of samples was not ideal for either culture or sequencing.[24] Small intestinal fluid is mucoid, rendering it more difficult to isolate and culture small intestinal bacteria, or to extract DNA for microbial sequencing. By treating small intestinal aspirates with a mucolytic agent (dithiothreitol) yields for culture, library preparation, and sequencing increased.[24] In a large-scale study, subjects underwent upper endoscopy, followed by both culture and sequencing of small intestinal aspirates. The culture data clearly identified that the ideal cutoff for SIBO was $>10^3$ CFU/mL.[25] This study also demonstrated, for the first time, that there was agreement between the identification of SIBO by breath testing (rise in H_2 of ≥ 20 ppm above baseline after ingestion of lactulose), culture, and sequencing, and the presence of clinical symptoms suggestive of SIBO.[25] In contrast, another recent study using the traditional aspiration technique (single lumen catheter) and definition of SIBO ($\geq 10^5$ CFU/mL) suggested that the association between SIBO and symptoms was not supported and that small bowel microbial changes in functional disorders might be related more to diet.[17]

Breath Testing

The use of breath testing in the diagnosis of SIBO has lacked universal acceptance. There are many reasons for this. Breath testing was never fully validated compared with culture of small intestinal aspirates. In addition, the usefulness of breath testing has been questioned. Some of the problems relate to the inconsistency with which breath testing is performed and interpreted. Some studies prefer glucose as the substrate, others lactulose. There are also wide discrepancies in thresholds for defining a positive breath test result. For example, studies suggest that a positive breath test for SIBO requires 2 H_2 peaks; this criterion has not been validated.

Finally, it must be stressed that breath testing is more complex than simply measuring H_2. Data now show that CH_4 is also important. CH_4 is produced by methanogens, and 4 moles of H_2 are required to produce 1 mole of CH_4. The presence of CH_4 suppresses H_2 on the breath test. Fortunately, conventional breath testing measures both H_2 and CH_4.

Best Practice Advice 6

Controversy remains concerning the role of SIBO in the pathogenesis of common functional symptoms, such as those regarded as components of IBS.

There has been controversy surrounding the role of SIBO in the pathogenesis of symptoms of functional bowel disorders such as IBS. A recent systematic review and meta-analysis concluded that SIBO was more common in IBS than in matched controls; on breath testing, the odds ratio for SIBO in patients with IBS was 4.9 and up to 33.5% of IBS subjects had SIBO based on culture compared with 8.2% in controls.[16] They also found that lactulose breath testing yielded a higher rate of positive results compared with culture or glucose breath testing.[16] Studies have also suggested that although SIBO is associated with IBS with diarrhea, CH_4-positive breath tests are linked to constipation-predominant IBS.[26]

Best Practice Advice 7

Management of SIBO should focus on the identification and correction (where possible) of underlying causes, correction of nutritional deficiencies, and the administration of antibiotics. This is especially important for patients with significant maldigestion and malabsorption.

For all the reasons already enumerated, the evaluation of the subject with suspected SIBO should involve the detection of related nutritional consequences as well as the identification of potentially correctable predisposing factors,

Table 2. Antibiotic Regimens for Treatment of Small Intestinal Bacterial Overgrowth

Antibiotic	Regimen
Amoxicillin-clavulanic acid	500/125 mg tid
Ciprofloxacin	250 mg bid
Doxycycline	100 mg bid
Metronidazole	250 mg tid
Neomycin	500 mg bid
Norfloxacin	800 mg daily
Rifaximin	800–1200 mg daily in divided doses
Tetracycline	250 mg qid
Trimethoprim-sulfamethoxazole	1 double strength bid

Table 3. Takeaway Points for the Clinician

Category	Takeaway point
Symptoms	Bloating and gas have been thought to be traditional symptoms of SIBO
	However, evidence suggests unexplained diarrhea might be more important
Signs	Although malabsorption (steatorrhea and vitamin deficiency) can be seen in SIBO, this is uncommon in the absence of blind loops or other structural causes of SIBO
Causes of SIBO	There are a number of causes of SIBO
	A good rule is to consider SIBO any time there is small intestinal stasis
	There is evidence for SIBO being present in a subset of IBS subjects
Diagnosis	Culture is considered the gold standard with new guidance suggesting a cutoff of $>10^3$ CFU of coliforms/mL in duodenal aspirates.
	Breath testing (lactulose and glucose) is most commonly used to diagnose SIBO and appears to identify subjects likely to respond to treatment
	Methane on breath testing is defined differently and now termed *intestinal methanogen overgrowth*
Treatment	Antibiotics are currently the mainstay of treatment

such as a blind loop, small bowel stricture, or coloenteric fistula. When, as is more often the case, the underlying problem cannot be corrected, attention should focus on the correction of any nutritional deficits.

Practice Advice 8

Although IBS has been shown to respond to therapy with a poorly absorbed antibiotic, the role of SIBO or its eradication in the genesis of this response warrants further confirmation in randomized controlled trials.

Phase 3 studies support a role for the minimally absorbed antibiotic rifaximin in the management of IBS with diarrhea.[27,28] Although the precise mode of action of rifaximin in IBS remains to be defined, there is now evidence that the response to rifaximin might be related to the presence of SIBO[29]; those with a positive breath test at baseline were more likely (59.7%) to improve compared with those with a negative breath test (29.8%).

The limitation of these recent data is that breath testing was only conducted in a small subset of subjects with IBS. In addition, it is important to recognize that conducting large-scale trials to treat SIBO and examine its impact on conditions such as IBS could not have been conducted reliably 3–4 years ago. Recent consensus documents and guidelines on SIBO testing have provided a framework for standardizing breath testing and interpretation.[10,11]

Best Practice Advice 9

There is a limited database to guide the clinician in developing antibiotic strategies for SIBO, in any context. Therapy remains, for the most part, empiric, but must be ever mindful of the potential risks of long-term broad-spectrum antibiotic therapy.

The goal of antibiotic therapy in SIBO is not to eradicate small intestinal microbiota but to modulate them in a manner that leads to symptomatic improvement. Ideally, the choice of antimicrobial agents should reflect in vitro susceptibility testing, this is usually impractical as different bacterial species, with different antibiotic sensitivities typically coexist. Antibiotic treatment remains, therefore, primarily empirical. Furthermore, the data to support any one antibiotic regimen are limited. In principle, an effective antibiotic regimen should cover both aerobic and anaerobic enteric bacteria. A list of antibiotic regimens that have been used in SIBO is provided in Table 2. How long to treat for? Here again, there is limited guidance. In general, a single 7- to 10-day course improves symptoms for up to several months in 46%–90% of patients with SIBO and renders breath tests negative in 20%–75%.[11,30,31]

Rifaximin has been the subject of a number of randomized controlled trials; a recent meta-analysis reported an overall 70% eradication rate for rifaximin in SIBO[14]; dosing ranged from from 800 mg/d for 4 weeks to 1200 mg/d for 7 days.[32–34] One practical challenge faced by clinicians in the United States is that SIBO is not a recognized indication for this antibiotic and might not be covered by the patient's insurance carrier.

How does one manage so-called intestinal methanogen overgrowth? One uncontrolled trial suggested that the combination of neomycin and rifaximin might be effective.[35]

Recurrence after 1 course of antibiotic therapy remains an issue (up to 44% at 9 months) and is more likely among older subjects, those who have undergone an appendectomy, and those with a history of chronic proton pump inhibitor use.[36] Because of recurrent symptoms, some patients will need repeated (eg, the first 5–10 days of every month) or continuous courses of antibiotic therapy. For the latter, rotating antibiotic regimens are recommended to prevent the development of resistance. Decisions on management should be individualized and also consider such risks as diarrhea, *Clostridium difficile* infection, intolerance, and cost. It is not necessary to repeat diagnostic tests for SIBO after antibiotic therapy should gastrointestinal symptoms respond.

Conclusions

Although there is much to do to determine the ideal approach to SIBO, recent work provides the foundation for

standardizing definitions and outcomes to allow for better controlled studies in the future (Table 3).

References

1. Card WI. Blind loop syndrome. Proc R Soc Med 1959; 52:28–31.
2. Donaldson RM Jr. Studies on the pathogenesis of steatorrhea in the blind loop syndrome. J Clin Invest 1965; 44:1815–1825.
3. Drasar BS, Shiner M, McLeod GM. Studies on the intestinal flora. I. The bacterial flora of the gastrointestinal tract in healthy and achlorhydric persons. Gastroenterology 1969;56:71–79.
4. Drasar BS, Shiner M. Studies on the intestinal flora. II. Bacterial flora of the small intestine in patients with gastrointestinal disorders. Gut 1969;10:812–819.
5. Gorbach SL. Intestinal microflora. Gastroenterology 1971;60:1110–1129.
6. King CE, Toskes PP. Small intestine bacterial overgrowth. Gastroenterology 1979;76:1035–1055.
7. Roberts SH, James O, Jarvis EH. Bacterial overgrowth syndrome without "blind loop": a cause for malnutrition in the elderly. Lancet 1977;2:1193–1195.
8. Levitt MD. Production and excretion of hydrogen gas in man. N Engl J Med 1969;281:122–127.
9. Metz G, Gassull MA, Drasar BS, et al. Breath-hydrogen test for small-intestinal bacterial colonisation. Lancet 1976;1:668–669.
10. Rezaie A, Buresi M, Lembo A, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: The North American Consensus. Am J Gastroenterol 2017;112:775–784.
11. Quigley EMM. Symptoms and the small intestinal microbiome—the unknown explored. Nat Rev Gastroenterol Hepatol 2019;16:457–458.
12. Pimentel M, Saad RJ, Long MD, et al. ACG clinical guideline: small intestinal bacterial overgrowth. Am J Gastroenterol 2020;115:165–178.
13. Choung RS, Ruff KC, Malhotra A, et al. Clinical predictors of small intestinal bacterial overgrowth by duodenal aspirate culture. Aliment Pharmacol Ther 2011; 33:1059–1067.
14. Gatta L, Scarpignato C. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. Aliment Pharmacol Ther 2017;45:604–616.
15. Wijarnpreecha K, Werlang ME, Watthanasuntorn K, et al. Obesity and risk of small intestine bacterial overgrowth: a systematic review and meta-analysis. Dig Dis Sci 2020; 65:1414–1422.
16. Ford AC, Spiegel BM, Talley NJ, et al. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2009;7:1279–1286.
17. Saffouri GB, Shields-Cutler RR, Chen J, et al. Small intestinal microbial dysbiosis underlies symptoms associated with functional gastrointestinal disorders. Nat Commun 2019;10:2012.
18. Montalto M, Santoro L, Dalvai S, et al. Fecal calprotectin concentrations in patients with small intestinal bacterial overgrowth. Dig Dis 2008;26:183–186.
19. Marie I, Leroi AM, Menard JF, et al. Fecal calprotectin in systemic sclerosis and review of the literature. Autoimmun Rev 2015;14:547–554.
20. Ricci JERJ, Chebli LA, Ribeiro T, et al. Small-Intestinal bacterial overgrowth is associated with concurrent intestinal inflammation but not with systemic inflammation in Crohn's disease patients. J Clin Gastroenterol 2018; 52:530–536.
21. Oliveira RB, Martinelli ALC, Troncon LEA, et al. Small intestinal bacterial overgrowth (SIBO) and vitamin K-responsive coagulopathy: a previously unrecorded association. BMJ Case Rep 2018 Jun 6;2018: bcr2017223531.
22. Giuliano V, Bassotti G, Mourvaki E, et al. Small intestinal bacterial overgrowth and warfarin dose requirement variability. Thromb Res 2010;126:12–17.
23. Khoshini R, Dai SC, Lezcano S, et al. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. Dig Dis Sci 2008;53:1443–1454.
24. Leite G, Morales W, Weitsman S, et al. Optimizing microbiome sequencing for small intestinal aspirates: validation of novel techniques through the REIMAGINE study. BMC Microbiol 2019;19:239.
25. Leite G, Villanueva-Millan MJ, Celly S, et al. 4 - First large scale study defining the characteristic microbiome signatures of small intestinal bacterial overgrowth (SIBO): detailed analysis from the Reimagine study. Gastroenterology 2019;156:S1–S2.
26. Kunkel D, Basseri RJ, Makhani MD, et al. Methane on breath testing is associated with constipation: a systematic review and meta-analysis. Dig Dis Sci 2011; 56:1612–1618.
27. Pimentel M, Lembo A, Chey WD, et al; TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011; 364:22–32.
28. Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology 2016;151:1113–1121.
29. Rezaie A, Heimanson Z, McCallum R, et al. Lactulose breath testing as a predictor of response to rifaximin in patients with irritable bowel syndrome with diarrhea. Am J Gastroenterol 2019;114:1886–1893.
30. Pittman N, Rawn SM, Wang M, et al. Treatment of small intestinal bacterial overgrowth in systemic sclerosis: a systematic review. Rheumatology (Oxford) 2018; 57:1802–1811.
31. Adike A, DiBaise JK. Small intestinal bacterial overgrowth: nutritional implications, diagnosis, and management. Gastroenterol Clin North Am 2018;47:193–208.
32. Lauritano EC, Gabrielli M, Scarpellini E, et al. Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. Eur Rev Med Pharmacol Sci 2009; 13:111–116.

33. Majewski M, Reddymasu SC, Sostarich S, et al. Efficacy of rifaximin, a nonabsorbed oral antibiotic, in the treatment of small intestinal bacterial overgrowth. Am J Med Sci 2007;333:266–270.
34. Yang J, Lee HR, Low K, et al. Rifaximin versus other antibiotics in the primary treatment and retreatment of bacterial overgrowth in IBS. Dig Dis Sci 2008;53:169–174.
35. Low K, Hwang L, Hua J, et al. A combination of rifaximin and neomycin is most effective in treating irritable bowel syndrome patients with methane on lactulose breath test. J Clin Gastroenterol 2010;44:547–550.
36. Lauritano EC, Gabrielli M, Scarpellini E, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. Am J Gastroenterol 2008;103:2031–2035.

Received May 20, 2020. Accepted June 1, 2020.

Correspondence
Address correspondence to: Eamonn M. M. Quigley, MD, FRCP, FACP, MACG, FRCPI, MWGO, Lynda K and David M. Underwood Center for Digestive Disorders, Houston Methodist Hospital and Well Cornell Medical College, 6550 Fannin Street, SM1201, Houston, Texas 77030. e-mail: equigley@houstonmethodist.org.

Acknowledgments
This Expert Review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of the *Journal*.

Conflicts of interest
The authors disclose the following: E. M. M. Quigley serves as a consultant to 4D Pharma, Alimentary Health, Allergan, Biocodex, Ironwood, Salix and Vibrant; receives research support from 4D Pharma, Biomerica, Takeda, Vibrant and Zealand; and holds patents with and equity in Alimentary Health. J. A. Murray received grant support from ImmusanT Inc, Allakos Inc, Oberkotter Foundation, Cour Inc; is a consultant to Bionix, Lilly Research Laboratory, Johnson & Johnson, Dr. Schar USA Inc, UCB Biopharma, Innovate Biopharmaceuticals, Glenmark Pharmaceuticals, Celimmune, Amgen, Intrexon Corporation, Kanyos, and Boehringer Ingelheim; holds patents licensed to Evelo Biosciences Inc; and receives royalties from Torax Medical. M. Pimentel serves as a consultant and received grant support from Salix Pharmaceuticals. M. Pimentel also consults for US Medical and Shire. M. Pimentel has equity and consults for Gemelli Biotech, Naia Pharmaceuticals, and Synthetic Biologics. Cedars-Sinai has a licensing agreement with Bausch Health, Naia Pharmaceuticals, Synthetic Biologics and Gemelli Biotech.